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Basal Plus Trial

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OBJECTIVE—Effective and easily implemented insulin regimens are needed to facilitate hospital glycemic control in general medical and surgical patients with type 2 diabetes (T2D).

RESEARCH DESIGN AND METHODS—This multicenter trial randomized 375 patients with T2D treated with diet, oral antidiabetic agents, or low-dose insulin (<0.4 units/kg/day) to receive a basal-bolus regimen with glargine once daily and dulaglutide before meals, a basal plus regimen with glargine once daily and supplemental doses of glulisine, and sliding scale regular insulin (SSI).

RESULTS—Improvement in mean daily blood glucose (BG) after the first day of therapy was similar between basal-bolus and basal plus groups (P = 0.16), and both regimens resulted in a lower mean daily BG than did SSI (P = 0.04). In addition, treatment with basal-bolus and basal plus regimens resulted in less treatment failure (defined as >2 consecutive BG >240 mg/dL or a mean daily BG >240 mg/dL) than did treatment with SSI (0 vs. 2 vs. 19%, respectively, P < 0.001). A BG <70 mg/dL occurred in 16% of patients in the basal-bolus group, 13% in the basal plus group, and 3% in the SSI group (P = 0.02). There was no difference among the groups in the frequency of severe hypoglycemia (<40 mg/dL, P = 0.76).

CONCLUSIONS—The use of a basal plus regimen with glargine once daily plus corrective doses with glulisine before meals resulted in glycemic control similar to a standard basal-bolus regimen. The basal plus approach is an effective alternative to the use of a basal-bolus regimen in general medical and surgical patients with T2D.

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Inpatient hyperglycemia in patients, with or without diabetes, is associated with poor hospital outcomes, including prolonged hospital stay, infections, and disability after hospital discharge, and death (1–3). Several clinical trials in critically ill patients have reported that improvement of glycemic control reduces hospital complications (4–6), hospital stay, and mortality (6–8). In patients with T2D admitted to general medicine and surgery services, recent randomized, controlled trials have shown that treatment with a basal-bolus regimen results in significantly lower mean daily blood glucose (BG) and in a higher percentage of BG within target range than does treatment with sliding scale regular insulin (SSI) (9,10). In addition, in general surgical patients, the basal-bolus approach results in a significant reduction in the frequency of composite complications, consisting of postoperative wound infection, pneumonia, bacteremia, and acute renal and respiratory failure (10). On the basis of these results, clinical practice guidelines have recommended the use of the basal-bolus approach as the preferred insulin regimen for the management of patients with diabetes not in the intensive care unit (ICU) (11–13).

Despite the benefits of a basal-bolus regimen in improving glycemic control in non-critically ill patients (2,7,9,10,14), many health care providers and hospitalists are reluctant to integrate this approach into their clinical practice, probably because of its complexity and a fear of hypoglycemia (15–18). Because most patients in the hospital have reduced caloric intake as a result of medical illness or surgical procedures, we hypothesized that a single daily dose of basal insulin might result in similar glucose control and lower the rate of hypoglycemia relative to a basal-bolus regimen. Accordingly, we tested the efficacy and safety in general medical and surgical patients with T2D of a daily dose of basal insulin plus corrective doses with a rapid-acting insulin analog given by sliding scale (basal plus regimen) with a basal-bolus insulin regimen.
regimen with glargine once daily and fixed doses of glulisine before meals and also with SSI (no basal insulin) given four times.

**RESEARCH DESIGN AND METHODS**—In this multicenter, prospective, open-label, randomized study, we enrolled 375 adult patients admitted to general medicine and surgery services. We recruited patients with a known history of T2D and with a BG before randomization between 140 and 400 mg/dL, a known history of T2D for >3 months, age between 18 and 80 years, and treatment at home with diet alone, any combination of oral antidiabetic agents, or low-dose insulin therapy at a daily dose ≤0.4 units/kg before admission. On admission, we stopped oral antidiabetic agents, and BG was measured before meals and at bedtime. Patients were recruited when BG was >140 mg/dL. Patients treated with low-dose insulin before admission had the same insulin regimen continued and were invited to participate if BG exceeded 140 mg/dL. We excluded patients with an admission, patients with any BG >400 mg/dL before randomization or with a history of hyperglycemic crises, patients with hyperglycemia without a known history of diabetes, patients admitted to or expected to require ICU admission, patients undergoing cardiac surgery, patients receiving corticosteroid therapy, patients with clinically relevant hepatic disease or impaired renal function (serum creatinine ≥3.0 mg/dL), patients with a history of diabetic ketoacidosis (19), pregnant patients, and patients with any mental condition rendering them unable to give informed consent.

Patients were randomized according a 2:2:1 ratio to one of three regimens: a basal-bolus regimen with insulin glargine given once daily and glulisine before meals plus corrective doses of glulisine by sliding scale for BG >140 mg/dL (Lantus and Apidra; Sanofi), a basal plus regimen with a daily dose of glargine and corrective doses of glulisine by sliding scale before meals for BG >140 mg/dL, or SSI for BG >140 mg/dL. (Novolin R; Novo Nordisk). Patients in the basal-bolus group were started at a total daily dose (TDD) of 0.5 units/kg divided with half as insulin glargine once daily and half as insulin glulisine before meals. Patients in the basal plus group received 0.25 units/kg of glargine plus corrective doses of glulisine before meals. In patients ≥70 years of age and those with a serum creatinine ≥2.0 mg/dL, the starting TDD in the basal-bolus group was reduced to 0.3 units/kg in the basal-bolus, and TDD of glargine was reduced to 0.15 units/kg in the basal plus regimen (10,20). The goal of insulin therapy was to maintain fasting and premeal glucose concentrations between 100 and 140 mg/dL. The doses of insulin were adjusted daily according to protocol (Supplementary Table 1). During treatment, treatment failure was arbitrarily defined as a mean daily BG level >240 mg/dL or two consecutive values >240 mg/dL (9,10). In case of treatment failure, patients in the basal plus and SSI groups were switched to a basal-bolus regimen starting at a TDD of 0.5 units/kg (9,10).

This study was conducted at Grady Memorial Hospital, Emory University Hospital, and the Veterans Administration Medical Center in Atlanta, Georgia; Medical University of South Carolina Medical Center in Charleston, South Carolina; and Tulane Medical Center in New Orleans, Louisiana. The study protocol and consent form were approved by the institutional review board at each participating institution. A research pharmacist at each institution followed a computer-generated randomization table to coordinate the randomization and treatment assignment. All patients were managed for medical and surgical problems by their primary care team, who received a copy of the assigned treatment protocol.

**Outcome measures**

The primary outcome of the study was difference in glycemic control, as measured by mean daily BG concentration, among patients treated with basal-bolus, basal plus, and SSI regimens (Fig. 1). Secondary outcomes included differences between treatment groups in any of the following measures: number of hypoglycemic events (BG <70 and <40 mg/dL) after the first day of treatment, number of episodes of hyperglycemia (BG >200 mg/dL) after the first day of treatment, TDD of insulin, hospital stay, and hospital complications. Also investigated were differences in glycemic control between medical and surgical patients.

**Statistical analysis**

This noninferiority study design was based on the hypothesis that the difference in mean daily BG between basal plus and basal-bolus would be no greater than 18 mg/dL (1 mmol/L) (9,10). A BG difference of such a magnitude has been reported as clinically insignificant and is typically smaller than the significant treatment effects detected in other superiority trials (9,10). In light of the data from the RABBIT 2 (Randomized Study of Basal-Bolus Insulin Therapy in the Inpatient Management of Patients With Type 2 Diabetes) medical and surgical trials (9,10), it is reasonable to assume that the SD of mean daily BG is bounded by 50 mg/dL. On the basis of two-sample t tests or Wilcoxon tests (one-sided, α = 0.05), 147 subjects were required for both the basal plus and the basal-bolus groups to ensure 80% power to reject the noninferiority hypothesis, with Bonferroni correction applied to adjust for multiple comparisons across four time points.

We compared baseline and clinical characteristics and outcomes, such as mean daily BG after day 1, occurrence of hypoglycemia, and occurrence of complications, both among treatment groups and between medical and surgical patients. The comparisons were made with the use of Wilcoxon tests (or Kruskal-Wallis tests) for continuous variables and χ² tests (or Fisher exact tests) for discrete variables. Multivariate analysis was conducted with a repeated measures linear model, which accounted for within-subject BG correlation through an autoregressive model of order 1 (AR 1) correlation structure. A P value <0.05 was considered significant. Statistical analyses were performed with SAS statistical software, version 9.2. The data are generally presented as mean ± SD for continuous variables and n (%) for discrete variables.

**RESULTS**—A total of 375 patients with T2D gave consent (210 medical and 165 surgical patients); of them, 22 patients were excluded from further analysis because they received <24 h of insulin treatment, were transferred to the ICU, or received corticosteroid therapy. A total of 146 patients in the basal-bolus group, 133 patients in the basal plus group, and 74 in the SSI group were included in the final analysis. The clinical characteristics of the study patients are shown in Table 1. There were no significant differences among groups in mean age, racial distribution, BMI, duration of diabetes, type of treatment before admission, or mean hospital stay. The most common admitting diagnoses in medical patients were cardiovascular (48%), infectious (17%), and pulmonary (14%) disorders, while the most common types of surgery were...
orthopedic (34%), abdominal (27%), and urologic (12%) procedures.

The mean admission glucose for the entire cohort was 204 ± 84 mg/dL, and the mean HbA1c was 8.4 ± 2.4%. The admission BG and HbA1c concentrations and changes in glycemic control during the hospital stay are shown in Table 2. All treatment regimens resulted in prompt and sustained improvement in mean daily BG concentration during the hospital stay. Treatment with basal-bolus and basal plus regimens resulted in similar improvements in daily BG after the first day of therapy (Fig. 1), and both regimens resulted in better glycemic control than did treatment with SSI (Table 2). The percentages of glucose readings >180 mg/dL were lower in the basal-bolus and basal plus groups than in the SSI group (27, 32, and 38%, respectively); however, the difference was not statistically significant (P = 0.11). In addition, SSI resulted in higher number of treatment failures than did the basal plus and basal-bolus regimens (19, 2, and 0%, respectively; P < 0.001).

We conducted repeated measures analysis with a linear mixed model to investigate the treatment effect during the hospital stay adjusted for a variety of factors, including participating institutions, hospital service (medicine vs. surgery), diabetes duration (>5 vs. ≤5 years), BG concentration at randomization (≤180 vs. >180 mg/dL), and admission HbA1c (≤7.5% vs. >7.5%). In this model, we observed that treatment with SSI versus basal bolus, a longer history of diabetes, a higher BG at randomization, and a higher HbA1c were significantly associated with worse glycemic control during the hospital stay. Compared with patients with glucose ≤180 mg/dL, those with a BG >180 mg/dL had significant higher mean daily glucose after the first day of therapy in the three treatment groups (all P < 0.001) and had a higher number of treatment failures (P = 0.006).

Similarly, the admission HbA1c level was found to correlate with inpatient glycemic control and response to treatment. Compared with patients with HbA1c <7.5%, those with HbA1c >7.5% had significant higher mean daily glucose: basal bolus, 142 ± 32 vs. 166 ± 35 mg/dL; basal plus, 147 ± 30 vs. 181 ± 37 mg/dL; and SSI, 152 ± 26 vs. 197 ± 43 mg/dL (all P < 0.001). In addition, treatment failures were more common in SSI-treated patients with HbA1c >7.5% (33% vs. 7%; P = 0.007).

The TDD of insulin was higher in the basal-bolus group (32.2 ± 16 units/day) than in the basal plus group (27.3 ± 11 units/day; P < 0.001), and both were higher than in the SSI group (8.2 ± 5 units/day; P < 0.001) (Table 2). There was no difference in the glargine daily dose between the basal-bolus and basal plus groups (21.1 ± 9 and 22.1 ± 8 units/day, respectively; P = 0.21); however, patients in the basal-bolus group received a higher dose of glulisine than did those in the basal plus group (17.1 ± 9 vs. 9.3 ± 6 units/day, respectively; P < 0.01).

There were no differences in the frequency of hypoglycemic events between basal-bolus and basal plus regimens. BG values <70 and <60 mg/dL were reported in 16 and 13% (P = 0.48) and in 8 and 5%, respectively (P = 0.43). The frequency of hypoglycemia was lower in the SSI group (3%) than in the glargine-based groups (P = 0.009) (Table 2). Severe hypoglycemia (<40 mg/dL) was uncommon and reported in 1% in the basal-bolus group, 1% in the basal plus group, and 0% in the SSI group (P = 0.76). The frequency of hypoglycemia was higher among patients treated with insulin before admission (22%) than among insulin-naive patients (9.9%; P = 0.01). In all cases, hypoglycemia was corrected with oral dextrose, and no episodes were associated with adverse outcomes.

**CONCLUSIONS**—This prospective, multicenter, randomized clinical trial compared the efficacy and safety of a daily dose of glargine plus corrective doses with
We observed that treatment with basal plus medical and surgical patients with T2D.

Recent clinical trials have also shown similar improvements in glycemic control, and both regimens resulted in better glycemic control and in a lower number of treatment failures than did SSI treatment.

The association between hyperglycemia and increased risk of hospital complications is well established in both ICU and non-ICU patients (3,4,6,8,21–23). Recent clinical trials have also shown treatment with a basal-bolus regimen to be superior to SSI alone in the management of patients with T2D. The RABBIT 2 medical trial (9) reported that a BG target of <140 mg/dL was achieved in two-thirds of patients treated with a basal-bolus regimen, whereas only one-third of those treated with SSI achieved target glycemia.

In general surgical patients, the RABBIT 2 surgical trial (10) reported improvement in glycemic control as well as a significant reduction in the frequency of hospital complications, including wound infection, pneumonia, bacteremia, and acute respiratory and renal failure (10). In this study, we report that the basal plus approach with a single dose of basal insulin plus corrective doses of rapid-acting insulin analogs before meals resulted in a similar improvement in mean daily BG to the basal-bolus regimen, with no difference in the number of treatment failures and similar numbers of hypoglycemic events, and the number of treatment failures in patients treated with a basal-bolus regimen compared with SSI treatment.

In agreement with previous studies (9,10,24), we show that the use of basal insulin alone or as part of a basal-bolus regimen is well tolerated with a lower rate of hypoglycemia. In the RABBIT 2 medical trial, 3% of patients in the basal-bolus group had a BG <60 mg/dL and no patients had a value <40 mg/dL (9). In the RABBIT 2 surgical trial, 12% of patients treated with basal-bolus regimen had a BG <60 mg/dL and 4% had a value <40 mg/dL (10). In the current study, a BG <60 mg/dL was seen in 8 and 3% of patients treated with basal-bolus or basal plus regimens, and only 1% had a BG <40 mg/dL. As previously reported, treatment with SSI resulted in a significantly lower rate of hypoglycemia (9,10). Minimizing hypoglycemic events is of major importance in hospitalized patients because it has been shown to be an independent risk factor of poor outcome (25–27).

The results of multivariate analysis indicate that the four more important factors associated with better glycemic control were the use of basal insulin versus SSI, duration of diabetes ≤5 years, a randomization BG ≤180 mg/dL, and an admission HbA1c ≤7.5%. Patients with BG >180 mg/dL and HbA1c >7.5% at admission had significant higher mean daily BG and experienced more treatment failures during therapy. This observation has important implications in clinical practice and indicates that T2D patients admitted with poor glycemic control (BG >180 mg/dL or HbA1c >7.5%) should be treated with basal-bolus or basal plus regimens, and the use of SSI alone should be avoided because a third of all patients will continue to have significant hyperglycemia, which may increase the risk of hospital complications (10).

We acknowledge the following limitations in this study. We excluded patients admitted to the ICU, those with clinically relevant hepatic disease or with serum creatinine ≥3.0 mg/dL, patients with severe hyperglycemia, and those receiving a total dose of insulin >0.4 units/kg/day before admission. For such patients, higher insulin doses or a standard basal-bolus approach may be the preferred approach in achieving glycemic control. In addition, our study was not powered to determine differences in hospital complications across groups. The recent RABBIT 2 surgical trial, which included a larger number of general surgical patients, reported a significant reduction in the frequency of hospital complications in patients treated with a basal-bolus regimen compared with SSI treatment (10). Finally, in this study we observed a lower rate of BG within target range compared with previous randomized

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**Table 1—Clinical characteristics of study patients**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Basal-bolus</th>
<th>Basal plus</th>
<th>SSI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>144</td>
<td>133</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>86 (60)</td>
<td>78 (59)</td>
<td>44 (59)</td>
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<tr>
<td>Female</td>
<td>58 (40)</td>
<td>55 (41)</td>
<td>30 (41)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.7 ± 11</td>
<td>58.6 ± 13</td>
<td>58.7 ± 12</td>
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</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32.6 ± 8</td>
<td>33.0 ± 9</td>
<td>32.6 ± 9</td>
<td></td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>96 ± 24</td>
<td>98 ± 28</td>
<td>95 ± 29</td>
<td></td>
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<tr>
<td>Duration of diabetes (years)</td>
<td>9.9 ± 8</td>
<td>7.6 ± 7</td>
<td>8.4 ± 7</td>
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<tr>
<td>Admission service</td>
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<td></td>
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<td></td>
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<tr>
<td>Medicine</td>
<td>82 (56)</td>
<td>76 (51)</td>
<td>40 (54)</td>
<td></td>
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<tr>
<td>Surgery</td>
<td>64 (44)</td>
<td>57 (43)</td>
<td>34 (46)</td>
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<tr>
<td>Hospital stay (days)</td>
<td>5.9 ± 5</td>
<td>6.0 ± 6</td>
<td>5.5 ± 5</td>
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<td>Admission diabetes therapy</td>
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<td>Diet alone</td>
<td>18 (12)</td>
<td>10 (8)</td>
<td>15 (20)</td>
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<td>Oral agents</td>
<td>99 (68)</td>
<td>98 (74)</td>
<td>54 (73)</td>
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<tr>
<td>Insulin alone</td>
<td>20 (14)</td>
<td>15 (11)</td>
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<tr>
<td>Insulin with oral agents</td>
<td>9 (6)</td>
<td>10 (8)</td>
<td>5 (7)</td>
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<td>Medical patients by primary admission diagnosis</td>
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<tr>
<td>Cardiovascular</td>
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<td>34 (45)</td>
<td>20 (53)</td>
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<tr>
<td>Pulmonary</td>
<td>15 (18)</td>
<td>10 (13)</td>
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<tr>
<td>Infection</td>
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<td>5 (13)</td>
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<tr>
<td>Cancer</td>
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<td>8 (11)</td>
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<td>Surgical patients by type of surgery</td>
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<td>Thoracic</td>
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<td>3 (6)</td>
<td>2 (7)</td>
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<tr>
<td>Urologic</td>
<td>7 (12)</td>
<td>7 (13)</td>
<td>3 (10)</td>
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<tr>
<td>Other</td>
<td>4 (7)</td>
<td>5 (9)</td>
<td>1 (3)</td>
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</table>

Data are mean ± SD or n (%).
inpatient trials, in which we observed 55% of BG within goal in patients treated with a basal-bolus regimen (9,10). In this trial, we followed a similar starting insulin dose and escalation protocol, increasing insulin dose by 10% if BG was between 140 and 180 mg/dL and by 20% if BG was >200 mg/dL. It is possible that increasing the starting insulin dose and increasing insulin titration will result in better glycemic control; however, it may also increase the risk of hypoglycemic events (28).

In summary, most general medical and surgical patients with T2D treated with diet, oral antidiabetic agents, or low-dose insulin (≤0.4 units/day) can be managed with a single daily dose of basal insulin with supplemental (corrective) doses of rapid-acting insulin analogous before meals. This basal plus regimen resulted in improvements in glycemic control and frequency of hypoglycemic events similar to those seen with a standard basal-bolus insulin regimen, and both regimens resulted in better glycemic control and in fewer treatment failures than did the use of SSI alone. These results indicate that basal insulin is necessary for stable glucose control in the hospital and that the basal plus approach is an effective alternative to the basal-bolus regimen for the initial management of hyperglycemia in general medical and surgical patients with T2D.

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G.E.U. wrote the initial research proposal and manuscript and collected and researched data. D.S., A.K., D.E.O., C.N., S.J., M.R., I.P., M.E.F., A.G., and V.A.F. reviewed and edited the research proposal and manuscript and contributed to the discussion. K.H. reviewed and edited the research proposal and manuscript, contributed to the discussion, and collected and researched data. D.R., I.P., M.E.F., V.H., and M.T.T. collected and researched data. G.E.U. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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